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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,878	08/24/2001	Nila Patil	HO-P02199US2	2515

31662 7590 02/05/2003

PERLEGEN SCIENCES, INC.
LEGAL DEPARTMENT
2021 STIERLIN COURT
MOUNTAIN VIEW, CA 94043

EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	11

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,878	PATIL ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement filed May 10, 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

2. Claims 1-3, 5 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Dong et al (U.S. Patent 6,361,947).

Dong teaches a method of analyzing a subset of nucleic acids within a nucleic acid population (see column 1) comprising:

(a) providing a population of nucleic acid fragments wherein at least some of the fragments have sequences that are repeated (See column 1, lines 48-51 and column 8, lines 64-68),

(b) denaturing said population of nucleic acid fragments (see figure 10, also see column 2, lines 20-24 and column 9, lines 17-18),

(c) incubating said denatured population of nucleic acids under conditions to produce doublestranded nucleic acids and single stranded nucleic acids where the conditions preferentially permit repeat sequence nucleic acid fragments to anneal (see column 2, lines 20-24 and column 9, lines 18-21)

(d) separating said single stranded subset of the population for the double stranded subset of the population of nucleic acid fragments (see column 9, lines 21-27 and figure 10),

(e) hybridizing said separated single stranded nucleic acids to probes on a nucleic acid probe array (see column 5, lines 57-60 and column 31, claim 1)

(f) determining which of the probes on the array hybridizes to the single stranded subset of the population thereby analyzing the single stranded subset of the population of nucleic acid fragments (see column 5, lines 57-60 and column 31, claim 1).

Dong teaches application of the method on human genomic DNA (see column 1, line 35) as well as the use of column chromatography for separation (see column 9, line 28).

3. Claims 15-20, 24, 26, 27, 30, 31 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Straus et al (Proc. Natl. Acad. Sci. (1990) 87:1889-1893).

Straus teaches a method of analyzing a subset of nucleic acids (see abstract) comprising:

(a) providing a driver population of nucleic acid and a tester population of nucleic acids (See page 1889, column 2, subheading "DNA" and figure 1),

(b) denaturing said population of tester and driver nucleic acids (see figure 1, also see page 1890, column 1, subheading "subtraction"),

(c) annealing the driver and tester populations to produce a single stranded subset of nucleic acids and a double stranded subset of nucleic acids (see page 1890, subheading "subtraction" and figure 1)

(d) immobilizing the driver population of nucleic acids by use of a biotin-streptavidin interaction to produce an unimmobilized single stranded tester subset of nucleic acids, an immobilized double stranded tester-driver subset of nucleic acids and an immobilized single stranded driver subset of nucleic acids (see page 1890, column 1, subheading "substraction" and figure 1),

(e) separating the unimmobilized single stranded tester subset of the nucleic acids from the single and double stranded driver subset of the nucleic acids (see page 1890, column 1, subheading "subtraction" and figure 1),

(e) hybridizing the unimmobilized single stranded tester nucleic acids to probes on a nucleic acid probe array (see page 1890, column 2, subheading "colony hybridization" and figure 3)

(f) determining which of the probes on the array hybridizes to the single stranded tester subset of the population thereby analyzing the single stranded subset of the

population of nucleic acid fragments (see page 1890, column 2, subheading "colony hybridization and figure 3).

Straus teaches that the tester and driver are from two different sources but are from the same species (see page 1889, columns 1 and 2).

Straus teaches repeating the method (see figure 1).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 4 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al (U.S. Patent 6,361,947) as applied to claims 1-3, 5 and 10 and further in view of Wigler et al (U.S. Patent 5,501,964).

Dong teaches the limitations of claims 1-3, 5 and 10 as discussed above. Dong does not teach screening fragments from human individuals or the use of two different human individuals or comparison of different species.

Wigler teaches comparison of DNA from two sources in order to determine the relationship between the sources (See column 3, lines 11-14) including comparisons between different individuals (see column 8, lines 40-48) as well as comparisons between different species (see column 21, example 7). Wigler expressly recognizes that any animal can be the source of the DNA, including mammals and non-mammals, as well as higher eukaryotes and humans.(see column 3, lines 62-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Dong with the different comparisons and DNA sources for comparison taught by Wigler since Wigler states

> "Comparative genomic DNA analysis holds promise for the discovery of sequences which may provide for information concerning polymorphisms, infectious DNA based agents, lesions associated with disease, such as cancer, inherited dominant and recessive traits, and the like. By being able to detect particular DNA sequences which have a function or affect a function of cells, one can monitor pedigrees, so that in breeding animals one can follow the inheritance of particular sequences associated with desirable traits. In humans, there is substantial interest in forensic medicine, diagnostics and genotyping, and determining relationships between various individuals. There is, therefore, substantial interest in providing techniques which allow for the detection of common sequences between sources and sequences which differ between sources. (Column 1, lines 23-37)."

An ordinary practitioner would have been motivated to apply the complexity reduction method of Dong on comparisons between individuals and between species in order to identify desirable traits, as expressly suggested by Wigler, as well as identifying

relationships between individuals and species as suggested by Wigler. An ordinary practitioner would have been motivated to remove the repeated sequences using the method of Dong in order to reduce the complexity of the comparison, in order to focus on a comparison of unique sequences rather than having the signal of unique sequence similarities and differences being swamped out by the larger repeat sequence signals.

7. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al (U.S. Patent 6,361,947) as applied to claims 1-3, 5 and 10 and further in view of Sundaram et al (J. Liquid Chromatography (1995) 18(5):925-939.

Dong teaches the limitations of claims 1-3, 5 and 10 as discussed above. Dong does not teach separation of single from double strands using hydroxyapatite or HPLC chromatography nor the use of phosphate buffer.

Sundaram teaches a method of separating single stranded DNA from double stranded DNA using hydroxyapatite chromatography and HPLC where the nucleic acids are eluted in phosphate buffer (see abstract and page 928).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to separate the single stranded DNA from the double stranded DNA since Dong notes "Methods of removing double stranded sequences will be known to those of skill in the art and may include without limitation, methods of digesting double stranded DNA such as double strand specific nucleases and exonucleases or methods of physical separation including, without limitation gel based electrophoresis or size chromatography. (See column 9, lines 2-28)." Since Dong suggests that any method in the art is desirable, it would further have been prima facie

obvious to utilize the method of Sundaram to achieve the goal of Dong since Sundaram states "This paper describes a practical and sufficiently sensitive HPLC method to isolate and separate the s.s. and d.s. DNA molecules present in calf thymus DNA standard by using Bio-Gel hydroxylapatite column and phosphate buffer as the mobile phase. The column was stable and proved reliable in the separation of DNA molecules (page 937)". An ordinary practitioner would have been motivated to fulfill the desire of Dong for separation of single and double stranded DNAs by the use of the practical, stable, sensitive and reliable method of Sundaram.

8. Claims 21-23, 25, 28, 29 and 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Straus et al (Proc. Natl. Acad. Sci. (1990) 87:1889-1893).as applied to claims 15-20, 24, 26, 27, 30, 31 and 38-40 and further in view of Wigler et al (U.S. Patent 5,501,964).

Straus teaches the limitations of claims 15-20, 24, 26, 27, 30, 31 and 38-40 as discussed above. Dong does not teach screening fragments from human individuals or the use of two different human individuals or comparison of different species.

Wigler teaches comparison of DNA from two sources in order to determine the relationship between the sources (See column 3, lines 11-14) including comparisons between different individuals (see column 8, lines 40-48) as well as comparisons between different species (see column 21, example 7). Wigler teaches that the sources can be cDNA, genomic DNA, restriction fragments of DNA or libraries (see column 2, lines 42-50). Wigler also teaches comparison of PCR amplified DNA (see column 4, lines 28-37). Wigler expressly recognizes that any animal can be the source of the

DNA, including mammals and non-mammals, as well as higher eukaryotes and humans.(see column 3, lines 62-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Straus to utilize the different comparisons and DNA sources for comparison taught by Wigler since Wigler states

> "Comparative genomic DNA analysis holds promise for the discovery of sequences which may provide for information concerning polymorphisms, infectious DNA based agents, lesions associated with disease, such as cancer, inherited dominant and recessive traits, and the like. By being able to detect particular DNA sequences which have a function or affect a function of cells, one can monitor pedigrees, so that in breeding animals one can follow the inheritance of particular sequences associated with desirable traits. In humans, there is substantial interest in forensic medicine, diagnostics and genotyping, and determining relationships between various individuals. There is, therefore, substantial interest in providing techniques which allow for the detection of common sequences between sources and sequences which differ between sources. (Column 1, lines 23-37)."

An ordinary practitioner would have been motivated to apply the tester driver method of Straus on comparisons between individuals and between species in order to identify desirable traits, as expressly suggested by Wigler, as well as identifying relationships between individuals and species as suggested by Wigler. An ordinary practitioner would have been motivated to focus on a comparison of unique sequences as taught by Straus in the broad variety of contexts suggested by Wigler.

Further, with regard to the order of the steps of immobilization, annealing and denaturation, as MPEP 2144.04 notes "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results". In this case, this is particularly true since the order of the steps would not be expected to impact the

results of the method. Whether immobilization was performed prior to the annealing or denaturation steps would not be expected to effect the reaction since the interaction is between the nucleic acids, which are equally available whether immobilized or not.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

January 31, 2003